Dangerous Liaisons: The Intersection of Diabetes and Hepatitis C Virus

Jorge Mera, MD, FACP
Objective

• Describe: The epidemiology of HCV in Indian Country and the association with diabetes

• Learn: How to stage liver fibrosis in HCV and plan for treatment

• Educate: Patients on the causes and effects of infection with the hepatitis C virus – transmission, disease processes and sequela

• Integrate: HCV screening with existing patient care services
Outline (1)

1. Epidemiology of HCV in the US
2. The intersection between HCV and DM
3. Evaluation of HCV and NAFLD
HCV Statistics in the United States

• An estimated 2.4 million people in the United States are living with HCV during 2013-2016
• An estimated 57,500 acute hepatitis C cases occurred in 2019
  • The number of estimated cases reported during 2019 corresponded to a 14% increase from the
    50,300 estimated cases reported during 2018, and a 133% increase from the 24,700 estimated
    cases reported during 2012
• HCV disease and complications are estimated to account for over 15,000 US deaths annually
  • HCV infections increases not only liver disease mortality rate but also cardiovascular an all-cause
    mortality
• Native Americans have higher rates of HCV infection than the general population
  • And higher rates of mortality from HCV than any other racial/ethnic group
• HCV is a systemic diseases
  • With Type 2 Diabetes Mellitus being one of the most common extra hepatic manifestations
HCV: Transmission

• Blood
  • IVDU is the leading cause in the United States
  • Snorting
  • Percutaneous injuries
  • Dental
  • Tattooing
  • Blood transfusion (Before 1992)

• Sexual contact
  • Rare in heterosexual
  • More frequent in HIV + MSM

• Mother-to-child
  • The rate is 1.7% - 4.3 %
  • Increased in IVDU, HIV co-infection, VL (?)

*Nosocomial; Health-care work; Perinatal

Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2018.
HCV and Injection Drug Use

Today > 80% of HCV Transmission Occurs in PWID

Viral Hepatitis Surveillance

Number of reported acute hepatitis C cases and estimated infections* — United States, 2012–2019

Number of newly reported* chronic hepatitis C cases† by sex and age — United States, 2018 (N=137,713)

Source: CDC, National Notifiable Diseases Surveillance System.

*The number of estimated viral hepatitis infections was determined by multiplying the number of reported cases by a factor that adjusted for underascertainment and under-reporting. The 95% bootstrap confidence intervals for the estimated number of infections are shown in the Appendix.
Acute Hepatitis C in the US

Rates of reported acute hepatitis C, by race/ethnicity — United States, 2003–2018

- American Indian/Alaska Native
- Asian/Pacific Islander
- Black, Non-Hispanic
- White, Non-Hispanic
- Hispanic

Rates of reported acute hepatitis C, by age group — United States, 2004–2019

0-19 yrs, 20-29 yrs, 30-39 yrs, 40-49 yrs, 50-59 yrs, 60 yrs and over

Source: CDC, National Notifiable Diseases Surveillance System.
2019 VIRAL HEPATITIS SURVEILLANCE REPORT (1)

Source: CDC, National Center for Health Statistics, Multiple Cause of Death 2019 on CDC WONDER Online Database.
2019 VIRAL HEPATITIS SURVEILLANCE REPORT (2)

Source: CDC, National Center for Health Statistics, Multiple Cause of Death 2019 on CDC WONDER Online Database.
American Indian/Alaska Native (AI/AN) Statistics in the United States

- 573 Federally recognized tribes
- 5.2 million AI/AN alone or in combination
- California and Oklahoma have the highest rate of AI/AN population

Hepatitis C in AI/AN in the US

- HCV disproportionately affects AI/AN1,2
- The AI/AN HCV mortality rate is 10.8 deaths per 100,000, compared to 4.5 per 100,000 nationally.
- From 2015 to 2016, incidence rates of acute HCV among AI/ANs rose from 1.8 to 3.1 cases per 100,000.
- Rates of chronic liver disease and cirrhosis deaths are 2.3 times higher among AI/ANs than Whites.

Natural history following initial infection with HCV

- Few or no symptoms; can progress without signs for decades\(^1\)
- Most pts asymptomatic until serious liver complications arise\(^2\)
What are the chances of someone with HCV infection developing cirrhosis or liver cancer?

• Rates of progression to cirrhosis are increased in the presence of a variety of factors, including
  • Being male
  • Being age >50 years
  • Consuming alcohol
  • Having nonalcoholic fatty liver disease, hepatitis B, or HIV coinfection
  • Receiving immunosuppressive therapy
  • Having diabetes (also increases risk of decompensated cirrhosis)
Outline (2)

1. Epidemiology of HCV in the US
2. The intersection between HCV and Diabetes
3. Evaluation of HCV and NAFLD
HCV: Extrahepatic Manifestations

• ~ 40% of HCV patients will develop at least one extrahepatic manifestation
• Often not clinically recognized
• Many patients do not have concurrent evidence of liver disease

Patrice Cacoub. Extrahepatic manifestations of chronic hepatitis C virus infection. NEJM March 18, 2021

- American Indian/Alaska Native: 15.1%
- Asian: 8.0%
- Hispanic: 12.1%
- Black, non-Hispanic: 12.7%
- White, non-Hispanic: 7.4%

Notes: Percentages are age-adjusted to the 2000 US standard population. Figure adapted from the National Diabetes Statistics Report, 2017. Data sources: 2013–2015 National Health Interview Survey and 2015 Indian Health Service National Data Warehouse (American Indian/Alaska Native data).
Diabetes and Liver Disease

Diabetes *aggravates* liver disease...

Individuals with *chronic HCV infection* had a **threelfold risk** of developing diabetes compared to those *without HCV*
- This has been described in both *cirrhotic* and in *non-cirrhotic*
- Prevalence of diabetes in *noncirrhotic* HCV patients was 12.6–17%
- HCV may *directly* induce impaired glucose tolerance and steatosis

Type 2 DM is a risk factor for chronic liver disease possibly through enhancement of:
- Inflammation through various cytokines and proinflammaratory factors
- Fibrosis (cirrhosis)

Diabetes is an independent predictor of:
- Decompensated cirrhosis
- Hepatocellular carcinoma

Liver disease can aggravate diabetes...

Diabetes can occur as a complication of cirrhosis, known as hepatogenous diabetes

Most people with cirrhosis have impairment of glucose tolerance
- Clinically overt diabetes is present in 30% of patients with liver cirrhosis
- 80% of patients with *normal fasting blood glucose* show impaired glucose

The prevalence of diabetes is:
- Significantly higher among patients with *HCV cirrhosis* than in patients with cirrhosis due to other etiologies
- Most studies have noted a 2- to 10-fold increase of T2D in chronic HCV infection compared to other liver diseases

HCV and Diabetes: Pathogenesis (1)

AKT: Protein Kinase B
IRS: Insulin Receptor Substrate
Glut-4: Glucose transporter 4

Hum J, Jou, JH. (2018), Clinical Liver Disease, 11:73-76
HCV and Diabetes: Pathogenesis (2)

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HCV and Diabetes: Pathogenesis (3)

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Hum J, Jou, JH. (2018), Clinical Liver Disease, 11:73-76
HCV and Diabetes: Pathogenesis (6)

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HCV and Diabetes: Pathogenesis (7)

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Hum J, Jou, JH. (2018), Clinical Liver Disease, 11:73-76
Outcomes of hepatitis C treatment on type 2 diabetes

How different is managing type 2 diabetes before and after hepatitis treatment?

• Lit search
  • Many case / cohort reports
The Effect of Viral Clearance Achieved by Direct-Acting Antiviral Agents on Hepatitis C Virus Positive Patients with Type 2 Diabetes Mellitus: A Word of Caution after the Initial Enthusiasm

1. Does SVR achieved by DAAs significantly prevent the onset of insulin resistance (IR) and Diabetes Mellitus (DM)?
   - Most of the studies conducted on patients who were treated with DAAs indicated a beneficial effect of SVR in reducing the risk of onset of IR/DM
     - Appropriate follow-up is still on the lasting efficacy of DAAs regarding the incidence of glucometabolic abnormalities

2. Does HCV clearance with DAAs lead to significant improvement of glycol-metabolic control in patients with diabetes? If so, is this control maintained over the long term?
   - In some groups, most studies published so far show an improvement of glucometabolic control at the end of therapy
   - Whether this beneficial effect is maintained over the long term is still unknown

3. Does SVR-related glucometabolic improvement induce de-escalation/withdrawal of antidiabetic therapy?
   - Most of the studies showed reduction/suspension of antidiabetic therapy in a minority of patients.
     - It has been suggested that diabetic patients with DAA-induced SVR should be carefully monitored in order to avoid hypoglycemic episodes

4. Do DAA-induced glycemic changes determine a significant clinical impact on the outcome of diabetes and its complications?
   - Studies have shown that SVR from treatment with INF or DAAs result in significant reductions in mortality (from any cause) and in the incidence HCC

5. What is the clinical impact of DAA-induced SVR on the incidence of HCC in diabetic patients?
   - Most likely the magnitude of risk reduction in HCC incidence found among diabetic patients with SVR is probably comparable to that observed in nondiabetics

J of Clin Med Feb 2020
Summary

• Chronic HCV with or without cirrhosis can lead to or worsen diabetes
• Achieving SVR with treatment can prevent or improve diabetes in some patients
  • Less likely with longstanding HCV and more extensive fibrosis
  • This may result in need for less medication for diabetes management
    • Close monitoring suggested for those on diabetes medications (especially insulin & sulfonylureas)
    • The duration of the improved glycemia is uncertain (more data needed)
• Achieving SVR from HCV can reduce complications for people with diabetes
  • Unclear if this is due to improved glycemia and/or reduced extra-hepatic effects of HCV due SVR
• Ongoing surveillance for Hepatocellular Carcinoma (HCC) still required
Outline (3)

1. Epidemiology of HCV in the US
2. The intersection between HCV and DM
3. Evaluation of HCV and NAFLD
HCV Workflow

- Confirm Diagnosis
- Lab/Imaging workup
- Fibrosis Staging
- Critical Information
- Treatment
- Cure
- Surveillance
CDC is augmenting previous guidance with two new recommendations:

1) Hepatitis C screening at least once in a lifetime for all adults aged ≥18 years, except in settings where the prevalence of HCV infection is <0.1% and

2) Hepatitis C screening for all pregnant women during each pregnancy, except in settings where the prevalence of HCV infection is <0.1%.

3) The recommendation for HCV testing that remains unchanged is regardless of age or setting prevalence, all persons with risk factors should be tested for hepatitis C, with periodic testing while risk factors persist.

4) Any person who requests hepatitis C testing should receive it, regardless of disclosure of risk, because many persons might be reluctant to disclose stigmatizing risks.

Confirm the Diagnosis
Laboratory Workup

• HCV Quant (Viral Load) and Genotype
  • Viral load confirms active infection, may determine the duration of treatment, It defines cure, Does not predict liver disease progression
  • Genotype not always needed

• HAV, Hep and HIV serology
  • Order total Hep A total antibody or IgG antibody if negative immunize
  • Order HBsAg, HBcAb (total or IgG) and HBsAb non-reactive, patient needs Immunization, if reactive monitor for HB reactivation
  • Important to treat HIV and monitor drug-drug interactions

• Complete Blood Count
  • Platelets are needed for liver fibrosis staging

• Comprehensive Metabolic Panel
  • ALT/AST are important for liver fibrosis staging, bilirubin is important for Child Pugh Score

• If Cirrhosis is present
  • Alpha fetoprotein to screen for HCC, and PT/INR to calculate MELD score

• Other optional tests
  • Urinary Drug Screen Iron profile, 25 OH Vitamin D, Iron panel
Liver Fibrosis: Biopsy

- F0: No fibrosis
- F1: Scattered portal fibrosis
- F2: Diffuse periportal fibrosis
- F3: Bridging fibrosis
- F4: Cirrhosis
  - Compensated
  - Decompensated
    - History or presence of ascites
    - Hx of esophageal bleeding due to esophageal varices
    - Hx or presence of hepatic encephalopathy
    - Jaundice

Non-Invasive Liver Fibrosis Staging in the Office

APRI: AST to Platelet Ratio Index

FIB-4 Index

An APRI score greater than 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis. APRI score greater than 0.7 had a sensitivity of 77% and specificity of 72% for predicting significant hepatic fibrosis.

A FIB-4 score <1.45 has a negative predictive value of 90% for advanced fibrosis. A FIB-4 >3.25 has a 97% specificity and a positive predictive value of 65% for advanced fibrosis.

Fibrotest/Fibrosure

Liver Fibrosis Staging by Imaging: Transient Elastography

The probe of the Fibroscan device is positioned in an intercostal space near the right lobe of the liver, and a 50-MHz wave is passed into the liver from a small transducer on the end of the probe. The device then measures the velocity of the shear wave (in meters per second) as this wave passes through the liver, and this measurement is converted to a liver stiffness measurement.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3594956/
# Fibrosis Staging Interpretation

<table>
<thead>
<tr>
<th>Metavir</th>
<th>Biopsy</th>
<th>Fibroscan</th>
<th>Fibrosure</th>
<th>APRI</th>
<th>FIB-4</th>
</tr>
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<tbody>
<tr>
<td>F4</td>
<td>F4</td>
<td>≥ 12.5 kPa</td>
<td>≥ 0.75</td>
<td>≥ 1.0</td>
<td>&gt; 3.25</td>
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<tr>
<td>F3</td>
<td>F3</td>
<td>9.6 12.4 kPa</td>
<td>0.58 – 0.74</td>
<td>&gt; 1.0</td>
<td>&gt; 3.25</td>
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<tr>
<td>F2</td>
<td>F2</td>
<td>7.1-9.5 kPa</td>
<td>0.49 – 0.57</td>
<td>&lt; 1.0</td>
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<tr>
<td>F1</td>
<td>F1</td>
<td>&lt; 7.0 kPa</td>
<td>0.23 – 0.48</td>
<td>&lt; 1.0</td>
<td>&lt; 1.45</td>
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<td>F0</td>
<td>F0</td>
<td>&lt; 7.0 kPa</td>
<td>&lt; 0.22</td>
<td>&lt; 1.0</td>
<td>&lt; 1.45</td>
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</tbody>
</table>
Fibrosis Staging Algorithm

HCC: Hepatocellular Carcinoma
Adapted from Boghal H, Sterling RK, Infect Dis Clin N Am 26 (2012) 839-847
Why is it Important to Stage Liver Fibrosis?

- Treatment will be different between those patients with decompensated and NOT decompensated cirrhosis

- All patients with liver fibrosis (F3 or F4) will need HCC surveillance

- All patients with liver fibrosis F4 will need screening for
  - Esophageal varices
  - Hepatic encephalopathy

- Patients with decompensated cirrhosis need to be referred to a liver transplant center
What does HCV treatment accomplish?

• SVR (cure) of HCV is associated with:
  • 70% Reduction of Liver Cancer
  • 50% Reduction in All-cause Mortality
  • 90% Reduction in Liver Failure

Lok A. NEJM 2012; Ghany M. Hepatol 2009; Van der Meer AJ. JAMA 2012
## HCV Therapies – Direct Acting Antivirals (DAAs)

<table>
<thead>
<tr>
<th>Medication</th>
<th>NS5B Inh</th>
<th>NS5A Inh</th>
<th>NS3/4A PI</th>
<th>Other</th>
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<td>Epclusa®</td>
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<td>velpatasvir</td>
<td>-</td>
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<td>velpatasvir</td>
<td>voxilaprevir</td>
<td>-</td>
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<tr>
<td>Mavyret®</td>
<td>-</td>
<td>pibrentasvir</td>
<td>glecaprevir</td>
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</tbody>
</table>

- **NS5B Inh** – Nonstructural protein 5B Polymerase Nucleotide Analog Inhibitor
- **NS5A Inh** – Nonstructural protein 5A Inhibitor
- **NS3 PI** – Nonstructural protein 3/4A Protease Inhibitor
Summary of Workflow

1. Positive HCV Ab
2. Positive Viral Load/Genotype
3. See patient, complete lab work-up, stage liver disease, order diagnostics as indicated
4. Order medication per algorithm, see patient at 4 and 8 weeks, test of cure 12 weeks after complete
NAFLD Workflow

- Recognizing NAFLD
- Staging NAFLD
- Referring to Hepatology
- Counseling and educating patients
NAFLD Definition

• Steatosis > 5% of hepatocytes by histological analysis or by MR-S
• No causes for secondary hepatic fat accumulation
• Once NAFLD diagnosis is made liver biopsy can differentiate between:
  Non-Alcoholic Fatty Liver (NAFL)
  Non-Alcoholic Steatohepatitis (NASH)

MR-S: Magnetic Resonance Spectroscopy

Slide credit: clinicaloptions.com
NAFLD

• Prevalence
  • In North America 24.13% of the general population is estimated to have NAFLD based on imaging (mostly US)
  • Among DM II population: 65-70% has NAFLD

• Natural history and outcomes
  • The most common cause of death in patients with NAFLD is cardiovascular disease
  • Liver-related mortality is the 12\textsuperscript{th} leading cause of death in general population, it is the second or third cause of death among patients with NAFLD
  • Cancer-related mortality is among the top three causes of death in subjects with NAFLD

• The most important prognostic indicator in NAFLD for increased risk of all-cause/ liver-related mortality is \textit{the presence and stage of fibrosis} rather than any distinction between steatosis and steatohepatitis
  • It takes about 14 years to progress to the next fibrosis stage in patients with NAFL
  • It takes 7 years to progress to the next fibrosis stage in patients with NASH
The NAFLD Continuum

NASH is a histologic diagnosis, requires biopsy
Noninvasive tests do not currently diagnose NASH

NAFLD

Normal Liver

Steatosis “NAFL”
- Fatty liver without inflammation or hepatocyte ballooning

Steatohepatitis “NASH”
- Fatty liver with inflammation and hepatocyte ballooning
- Increasing fibrosis leading to cirrhosis, hepatocellular carcinoma

Worldwide prevalence:
- ~ 25%
- 1.50% to 6.45%

Recognizing Natural History

Natural History of Nonalcoholic Fatty Liver Disease

100 patients with NAFLD

20+ yrs

5 develop cirrhosis

5-10 yrs

2-3 decompensate

1-5 yrs

1-2 liver-related death or transplant

95 (F0-3) (Never develop cirrhosis or hepatic complications)

+ 2-3 Cirrhosis without hepatic complications

97-98 Non-liver related death

Slide courtesy of Youssef Barbour M.D
Fatty Liver Is Not Benign: Mortality Associated With Isolated Steatosis and NASH

- Analysis of all-cause mortality in 6 separate studies among patients without NAFLD vs with and without NASH
  - NAFLD determined by ultrasound; NASH determined by liver biopsy

Who is at risk for NAFLD?

Risk Factors for NAFLD[1]

• Obesity
• Dyslipidemia
• Type 2 diabetes
• Metabolic syndrome
• Polycystic ovary syndrome

NAFLD Clinical Presentation

• **Symptoms**
  • Usually asymptomatic, majority discovered by chance
  • Fatigue frequently present

• **Often an “incidental finding”**
  • Incidental abnormal liver enzymes
  • Incidental “bright liver” on imaging
  • Incidental hepatomegaly

• **Common scenarios**
  • Statin monitoring
  • “Annual reviews” in T2DM/lipid/hypertension clinics
  • Medical insurance/occupational health checks

• **Normal Liver Enzymes Do Not Rule Out NASH**
  • NAFLD a common diagnosis in patients with “incidental” abnormal liver enzymes such as ALT, AST[1-3]
  • Liver enzymes may be normal in ~ 80% of NAFLD patients[4,5]
    • ALT and AST not sensitive for NAFLD/NASH
    • Poor correlation between ALT and histology
      • ALT typically decreases with advanced fibrosis
      • As NASH progresses, AST/ALT ratio may increase (ie, ALT < AST)

• **Histology severity similar in NAFLD patients with normal vs abnormal liver enzymes[6-8]**

Diagnosis of liver steatosis

- **US** is the most common way to detect steatosis.
  “*It lacks sensitivities in the morbidly obese and when the degree of liver fat infiltration is < 33% of hepatic content.*”

- **MRI based techniques** provide accurate and reproducible quantitative assessment of steatosis [can detect as little as 5% fat within the liver]

- **CAP**: Controlled Attenuation Parameter

### Other Causes of Steatosis

- Alcohol
- Hepatitis C virus, GT3
- Lipodystrophy
- Medications
- Malnutrition
- Hereditary disorders
  - Wilson disease (check 24-hr urine copper\(^{[2]}\))
  - Hypobetalipoproteinemia (check ApoB)
  - Lysosomal acid lipase deficiency

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Scores for Identifying Advanced Fibrosis in NAFLD: NAFLD Fibrosis Score and FIB-4

Imaging for Identifying Advanced Fibrosis in NAFLD: Vibration-Controlled Transient Elastography

- Accurate in detecting advanced fibrosis
- Most reliable in ruling out advanced hepatic fibrosis (NPV stronger than PPV)
- Predicts risk of decompensation and complications
- Correlates well with portal pressure
Percentage of Weight Loss Associated With Histologic Improvement in NAFLD

<table>
<thead>
<tr>
<th>Weight Loss</th>
<th>Outcome Among Patients Achieving Weight Loss</th>
<th>Patients Sustaining Weight Loss at 1 Yr[1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 10%[1]</td>
<td>Fibrosis regression (45% of patients)[1]</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>≥ 7%[1]</td>
<td>NASH resolution (64% to 90% of patients)*</td>
<td>18%</td>
</tr>
<tr>
<td>≥ 5%[1-3]</td>
<td>Ballooning/inflammation improvement (41% to 100% of patients)*</td>
<td>30%</td>
</tr>
<tr>
<td>≥ 3%[1-4]</td>
<td>Steatosis improvement (35% to 100% of patients)*</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*Depending on degree of weight loss.

Summary (2)

• AI/AN populations are disproportionately affected by HCV and DM
  • Chronic HCV with or without cirrhosis can lead to or worsen diabetes

• Achieving HCV SVR with treatment can:
  • Prevent or improve diabetes in some patients
  • Reduce complications for people with diabetes
  • Decreases liver related and all cause mortality

• NAFLD is not always benign; NASH is the progressive form of NAFLD

• Noninvasive tests can identify patients at high risk for NASH
  • NFS, FIB-4, VCTE
  • Patients with > F2 should be referred for liver biopsy

• NASH is a histological diagnosis
  • Although no medications are approved to treat NASH, weight loss with lifestyle modification can improve steatosis and fibrosis

• In patients with DM and HCV is important to rule out NAFLD once SVR has been obtained
Key Points

• NAFLD and NASH are very common in the clinical practice of primary care physicians

• Fatty liver is not always benign; NASH is the progressive form of NAFLD

• Noninvasive tests can identify patients at high risk for NASH
  • NFS, FIB-4, VCTE
  • Patients with > F2 should be referred for liver biopsy

• NASH is a histological diagnosis

• Although no medications are approved to treat NASH, weight loss with lifestyle modification can improve steatosis and fibrosis

• Many new drug regimens are being developed to treat NASH
References


7. World Health Organization (WHO). “Hepatitis C” Media Centre, Fact Sheet # 164, July 2015,


14. Sovaldi® [package insert]. Gilead Sciences, Foster City, CA

15. Harvoni® [package insert]. Gilead Sciences, Foster City, CA


20. Project ECHO. University of New Mexico. http://echo.unm.edu/

## Helpful Resources

<table>
<thead>
<tr>
<th>Resource</th>
<th>Description</th>
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<tbody>
<tr>
<td><a href="http://www.npaihb.org">npaihb.org</a></td>
<td>Text HCV 97779</td>
</tr>
<tr>
<td><a href="http://www.hcvguidelines.org/">hcvguidelines.org/</a></td>
<td>On-line curriculum on liver disease and HCV, includes clinical studies, clinical calculators, slide lectures</td>
</tr>
<tr>
<td><a href="http://www.hepatitisc.uw.edu/">hepatitisc.uw.edu/</a></td>
<td>ECHO guidelines</td>
</tr>
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